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LEFFERS JR, G	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/404,448	BYRNE ET AL.	
	Examiner	Art Unit	
	Jerry Leffers	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-60* is/are rejected.

7)☒ Claim(s) *53 and 57* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☒ Interview Summary (PTO-413) Paper No(s). *10* .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Acknowledgment is made of applicants' amendment filed 10/3/00, in which applicants canceled claims 1-27 and added new claims 41-60. Receipt is also acknowledged of a substitute declaration for Barry Byrne. This declaration appears to be properly executed and has been entered into the file. Finally, receipt is acknowledged of an amendment filed 12/14/00, in which applicants canceled claims 28-40. Claims 41-60 are pending in this application.

Any rejection of record not addressed herein has been withdrawn in view of applicants' arguments and amendments to the claims. As all of the claims have been rejected, and each of the new rejections was necessitated by applicants' amendment, this action is FINAL.

Claim Objections

These new objections to the claims are necessitated by applicants' amendment filed 10/3/00.

Claim 53 is objected to because of the following informalities: "AAv-2" should be amended to "AAV-2". Appropriate correction is required.

Claim 57 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 56 specifies a kit comprising a particular viral vector and

instructions for its use. Claim 57 merely specifies a kit comprising the recombinant vector of claim 56 and instructions for its use. It is unclear as to how claim 57 further limits claim 56.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention. **This rejection is maintained for reasons of record against claims 19, 23, and 27 in Paper No. 8, mailed 10/3/00 and repeated below.**

The application discloses a recombinant HSV-1/AAV hybrid virus (d27.1rc HSV-1) which is encompassed by the definitions for **biological material** set forth in 37 C.F.R. § 1.801. Because it is apparent that this biological material is essential for practicing the claimed invention, it must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809.

It is unclear whether this biological material is known and readily available to the public or that the written instructions are sufficient to reproducibly construct this biological material from starting materials known and readily available to the public. Accordingly, availability of such biological material is deemed necessary to satisfy the enablement provisions of 35 U.S.C. § 112. If this biological material is not obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological material. In order for a deposit to meet all criteria set forth in 37 C.F.R. §§ 1.801-1.809, applicants or assignee must provide assurance of compliance with provisions of 37 C.F.R. §§ 1.801-1.809, in the form of a declaration or applicant's representative must provide a statement. The content of such a declaration or statement is suggested by the enclosed attachment. Because such deposit will not have been made prior to the effective filing date of the instant application, applicant is required to submit a verified statement from a person in a position to corroborate the fact, which states that the biological material which has been deposited is the biological material specifically identified in the application as filed (37 C.F.R. § 1.804). Such a statement need not be verified if the person is an agent or attorney registered to practice before the Office. Applicant is also reminded that the specification must contain reference to the deposit, including deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.

Response to Arguments

Applicant's arguments filed 10/3/00 have been fully considered but they are not persuasive. Applicants' response argues essentially that construction of d27.1.rc HSV-1 has been

sufficiently described in the specification to enable one of skill in the art to construct the claimed invention. This is not an accurate assertion. The specification describes the construction of a particular virus, d27.1.rc HSV-1 by homologous recombination of a linearized fragment of a plasmid bearing the AAV-2 rep and cap sequences with an HSV virus comprising a specific deletion within the ICP27 gene (d27.1) and insertion of a thymidine kinase cassette (e.g. Figure 2). Contrary to the assertion made in the response, construction of d27.1 is not outlined on page 64 of the specification, nor is it clear that this viral construct is readily available to the public. Nor is it clear that the plasmid construct used to provide the sequences encoding AAV-2 rep and cap, pHSV-106rc, is readily available to the public. Absent a detailed description of the construction of d27.1 and in the absence of any demonstration that the d27.1 virus and pHSV-106rc plasmid is readily available to the public, it would require undue, unpredictable experimentation to construct a herpes simplex virus having the exact nucleotide sequence of that found in the d27.1.rc HSV-1 virus described in the specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 41-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. **These are new rejections necessitated by applicants' amendment filed 10/03/00.**

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 41 recites the broad recitation of "a recombinant herpes simplex virus ICP27 deletion mutant", and the claim also recites "(rHSV d27.1rc virus)" which is the narrower statement of the range/limitation.

As noted above, claims 41-45 comprise the limitation of "(rHSV d27.1.rc)". It is unclear from reading the specification and the language of these claims whether this limitation is meant to specify a specific recombinant virus which is described in the specification, or is meant to more generally specify a class of recombinant virus (e.g. a series of d27.1 constructs having rep/cap inserted into ICP27 with different promoters driving rep/cap transcription, and/or having

different AAV rep/cap sequences). It is unclear how, under the first interpretation of the recited limitation, how the virus described in the specification as d27.1.rc HSV-1 could also have rep and cap sequences under different heterologous promoters or how it could comprise rep and cap sequences from AAV-6, for example. If the second interpretation of the recited limitation is correct, then it would be remedial to amend the claim language for these claims to eliminate reference to a specific embodiment from the specification (i.e. rHSV d27.1.rc).

Claim 43 is vague and indefinite in that it comprises a period after the term "CMV 40", but prior to the end of the claim. Substitution of a comma in place of the period would be remedial.

Claims 45 and 53 are vague and indefinite in that there is no clear and positive prior antecedent basis for the phrase "wherein the adeno-associated virus is AAV-1, AAV-2, AAV-3 AAV-4, AAV-5 or AAV-6.". It would be remedial to amend these claims to indicate that the rep and cap sequences are obtained from a group consisting of these different viruses.

Claim 46 is vague and indefinite in that the phrase "..the mutant is a deletion or alteration..". It would be remedial to amend the claim language to specify "the mutant comprises a deletion or alteration..".

Claim 47 is vague and indefinite in that the term "gene product" is redundant for the subsequent term "ICP8 protein". It would be remedial to drop the term "gene product" from the claim language.

Claim 49 is vague and indefinite in that the claim is grammatically incorrect in its use of the term "is a". This term can be deleted from the claim language without altering the scope encompassed by the claim.

Claim 50 is grammatically incorrect in that the claim specifies an alteration in the IE63 gene "to overexpress ICP8". This phrasing implies intent on the part of a mutation which is not really appropriate. It would be more grammatically correct to specify something like "a mutation in immediate early gene IE63 effective to increase expression of ICP8 protein.".

Claim 51 is vague and indefinite in that the metes and bounds of the term "provides" are unclear. A more grammatically correct expression would be something like "results in" underexpression or lack of expression of ICP27. Also, the term is vague and indefinite in that the metes and bounds of the term "underexpression" of ICP27 are unclear. From reading the specification, it does not appear that this term is well defined with regard to functional criteria for "underexpression" of ICP27. It would be remedial to amend the claim language to more clearly indicate what is intended by the limitation of an "underexpression" of ICP27.

Claim 52 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "the herpes simplex virus is" in claim 50, upon which claim 52 is dependent.

Claim 56 is vague and indefinite in that the phrase "A kit comprising a virus vector comprising.." can be interpreted to specify a kit comprising a virus vector and also comprising the individual components which follow the phrase. It would be remedial to amend the claim

language to specify something like "A kit comprising a viral vector, said viral vector comprising...".

Claim 57 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "the recombinant virus" in claim 56, upon which claim 57 is dependent.

Claim 58 is vague and indefinite in that the phrase "..and coding sequences for AAV-2 replication proteins comprising proteins UL5, UL8, UL52 and UL29." implies the recited proteins are AAV proteins. The recited replication proteins are required for AAV-2 replication, but are actually HSV polypeptides encoded by HSV and presumably functioning in the HSV life cycle. It would be remedial to amend the claim language so as to not imply that the recited polypeptides are AAV polypeptides.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 46, 56-58 and 60 are rejected under 35 U.S.C. 102(b) as being anticipated by Dong et al (B1; see the entire document). **This is a new rejection necessitated by applicants' amendment of 10/03/00.**

Dong et al teach the construction of helper viruses for production of rAAV which comprise genes essential for AAV replication (Abstract). Dong et al teach that the helper viruses of their invention can be derived from adenovirus or one of several different types of viruses classified in a general class of "herpesvirus", including HSV (page 6, lines 16-28). Dong et al teach that these helper viruses can either be replication competent (i.e. comprising viral packaging and origin of replication sequences) or replication defective (page 15, lines 19-29). Dong et al specifically teach that the herpesvirus helper viruses of their invention will, generally speaking , comprise one or more of the AAV rep, lip and cap genes (page 7, lines 8-20). Dong et al teach that the essential AAV genes can be inserted into the helper virus genome at positions where either essential or non-essential genes from the helper virus genome have been deleted (page 7, lines 21-32). Dong et al teach that the helper viruses of their invention can promote the expression of the essential AAV genes with either "natural" AAV promoters (e.g. p5 from AAV) or heterologous promoters (e.g. immediate early promoter from CMV, retroviral LTR elements) (page 8, lines 20-27; page 9, lines 4-14). The reference teaches that the nature of the herpes family virus is not believed to be crucial to the successful practice of the invention (e.g. herpes simplex virus, cytomegalovirus, etc.) (page 32, line 20 to page 33, line 9). Dong et al teach a prophetic example for insertion of AAV rep, lip and/or cap sequences into the genome of HSV featuring the HSV vector R7020. R7020 features deletion of approximately 700 bp from the domain of the thymidine kinase gene and all of the sequences from the 3' end of the IE63 (α27) gene to the α4 gene in the reiterated sequence of the S component of the HSV genome. In

R7020, a cassette comprising HSV-2 gD, gG, gI and the tk gene under control of the α4 gene promoter has been inserted in place of the deleted sequences. The authors teach that the rep-lip-cap genes can be inserted in, at least, either of two positions including the site between the inserted tk gene and the HSV-2 DNA sequences and the site of the deletion of the natural tk gene (Example VI(1) page 44). It is noted that throughout their application, Dong et al do not distinguish between different strains of AAV for obtaining copies of rep-lip-cap genes for use in making the packaging constructs of their invention. Dong et al teach, however, at least one example wherein the rep-lip-cap sequences were obtained from an AAV-2 clone (Example 1, page 37, paragraph 1).

Response to Arguments

Applicants' arguments filed 10/3/00 in response to rejection of similar claims in Paper No. 8 under 35 U.S.C. 102(b) over Dong et al have been fully considered but they are not persuasive. Applicants' response essentially argues: 1) Dong et al speaks only globally of inserted expression regions comprising one or more rep, lip or cap genes and that there is no claim or description of a herpes virus engineered specifically with rep and cap genes, 2) the reference merely mentions that HSV may be used to construct helper virus by insertion of some number of AAV genes required for replication into the HSV genome and the reference does not disclose applicants' DNA segment, and 3) a reading of the reference as a whole at best provides only an "inherent" suggestion to supply the Rep, Lip and/or Cap proteins to cells by inserting rep, lip or cap into a herpes virus.

These arguments appear to be intended to demonstrate that the description of the claimed recombinant herpesviruses and vectors which express rep and cap in Dong et al was not enabling or was not sufficient to allow one of skill in the art to envision the claimed embodiments because there was no reduction to practice for the claimed inventions. On the contrary, given the skill of the art at the time of applicants invention, the Dong et al reference sufficiently described the claimed inventions such that one of skill in the art could envision these embodiments readily. An explicit, prophetic example is provided by Dong et al for insertion of essential AAV genes into the herpes virus genome in order to generate an HSV mutant expressing these genes (see Example 1, page 44). An actual reduction to practice for the claimed invention is not required for a reference to meet the written description and enablement requirements. The Dong et al reference was in fact enabling at the time of applicants invention to make and use the claimed inventions of a recombinant herpesvirus vector, virus or DNA segment comprising AAV rep and cap coding sequences under control of their own "natural" promoters or heterologous promoters. For example, the herpes viral sequences required for AAV-helper virus function were known in the art at the time of applicants invention as were the "natural" promoters for the AAV rep-lip-cap genes, p5, p19 and p40 (see Muzyczka, Seminars in Virology. 1991, Vol. 2, pages 281-290, see especially page 284-column 2-paragraph 1; Figure 1). It is noted that a recombinant herpesvirus comprising the herpes viral genes known to be necessary for AAV-helper function, and also comprising coding sequences for AAV rep and cap, is by definition a DNA segment comprising these coding sequences since herpesvirus is a DNA virus. It is also noted that the

rejected claims all feature open claim language (e.g. "A DNA segment comprising..." or "A recombinant herpes simplex virus mutant comprising...") such that an HSV helper virus construct comprising AAV rep-lip-cap sequences would necessarily meet the claim limitation of having AAV rep and cap coding sequences as well as the necessary UL5, UL8, UL52 and UL29 sequences. There is no limitation in the rejected claims that limits the AAV sequences in the HSV constructs to only AAV cap and rep. Thus, the Dong et al reference inherently discloses each and every element of the claimed inventions.

It might be concluded by some that because the Dong et al reference does not explicitly teach the limitations of the inclusion of the necessary helper proteins (i.e. UL5, UL8, UL52 and UL29) that the reference does not anticipate these embodiments of the claimed invention. For this reason, rejections of these claims under 35 U.S.C. 103(a) follow.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 56-58 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dong et al in view of Muzyczka (Seminars in Virology. 1991, Vol. 2, pages 281-290; see the entire document). **This is a new rejection necessitated by applicants' amendment filed 10/03/00.**

The teachings of Dong et al are described above and applied as before, except:

Dong et al do not explicitly teach the use of the HSV sequences UL5, UL8, UL52 and UL29 in their constructs.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include the known essential HSV genes for AAV packaging because Dong et al teach embodiments of their invention wherein a single HSV helper construct provides all of the required helper sequences and because Muzyczka teaches that the UL5, UL8, UL52 and UL29 sequences were the minimal HSV sequences required for helper function. One would have been motivated to do so in order to, as taught by Dong et al, practice their invention for HSV-mediated packaging of AAV such that all of the required HSV factors could be provided by one construct. Based on the entirety of the teachings above, and absent any evidence to the contrary, there

would have been a reasonable expectation of success in incorporating the recited HSV sequences into the constructs taught by Dong et al for HSV-mediated packaging of AAV.

Claims 41-48 and 50-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dong et al (B1) and Glorioso et al (B; see the entire reference). **This rejection is maintained for reasons of record in Paper No. 8, mailed 7/5/00 and repeated below.**

This rejection is applied to claims 41-45 in that it is unclear whether the term "rHSV d27.1rc" is meant as only an example of an ICP27 deletion mutant of the invention or whether the claims are directed solely to the embodiments comprising the d27.1 backbone. This rejection applies to the broader limitation of "A herpes simplex virus ICP27 deletion mutant..".

The teachings of Dong et al are described above and are applied as before, except:

Dong et al do not explicitly teach the alteration or deletion of the ICP27 gene for their HSV-1/AAV hybrid helper virus or vectors.

Glorioso et al teach the construction and use of a variety of HSV vectors (Abstract). Glorioso et al teach that the HSV genome is well characterized and that one can make deletion mutations in essential genes (in particular ICP4 & ICP27) such that the HSV vector is replication-defective unless grown in a host cell providing the missing translation product or products (column 2, paragraph 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the recombinant HSV vector taught by Dong et al to include a deletion of at least

part of the ICP27 gene because Dong et al teach that it is within the skill in the art to make the helper-virus constructs of their invention comprising deletions of any non-essential or essential gene (e.g. glypcoprotein H or ICP27) so long as the essential gene products are provided in trans during replication of the helper virus and because Glorioso et al specifically teach that it is possible and desirable to make recombinant HSV vectors comprising a deletion of at least a portion of the ICP27 gene. One would have been motivated to do so in order to receive the expected benefit of limiting the induction of herpes viral replication during the methods taught by Dong et al for production of rAAV with the HSV-helper vector. Absent any evidence to the contrary there would have been a reasonable expectation of success in incorporating a deletion in the ICP27 gene, as taught by Glorioso et al, in the recombinant HSV vectors taught by Dong et al for expression of AAV rep and cap during production of high-titre rAAV stocks.

Response to Arguments

Applicant's arguments filed 10/03/00 against the rejection of similar claims in Paper No. 8 have been fully considered but they are not persuasive. Applicants' response essentially argues: 1) the references supply neither motivation to combine or expectation of success, 2) motivation to experiment with deletions, deletions of different genes in HSV or with different constructs was a challenge to Applicants to improve rep and cap inducible cell lines because current procedures utilizing rep and cap plasmids had a tendency to generate wild-type AAV, and 3) despite knowledge of the genes involved, procedures for constructing expression vectors, and gene

modification techniques, others had not disclosed the recombinant AAV vectors that provided high titre rAAV production.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to combine the teachings of the two references comes from the fact that Dong et al teach preferred embodiments of their system for HSV-mediated packaging of rAAV particles wherein an HSV mutant comprising a mutation in any of one or more essential HSV genes needed for replication is used to provide copies of the essential rep-lip-cap sequences. Glorioso et al teach numerous mutants of HSV which comprise mutations in one or more essential HSV genes, many of which comprise mutations in ICP27. Glorioso et al teach that only two of the IE genes of HSV are required for HSV replication, ICP4 and ICP27, and that elimination of the expression of these genes results in the expression of only other immediate early loci . Such mutants require complementing cell lines for propagation of the HSV constructs (column 2, lines 26-39). One would have been motivated to make and use an HSV construct comprising a deletion in ICP4 and/or ICP27, as taught by Glorioso et al, in order to receive the expected benefit of limiting the induction of herpes viral replication during the

methods taught by Dong et al for production of rAAV with the HSV-helper vector (e.g. an ICP4/ICP27 double mutant as taught by Glorioso). By limiting such induction, one of ordinary skill in the art would expect to limit the expenditure of cellular resources for gene expression/viral production to the product of rAAV, with the added benefit of limiting production of contaminating HSV.

With regard to the assertion that there would have been no expectation of success in making such a vector from the combined teachings of Dong et al and Glorioso et al, there is no scientific reasoning or data provided to back up this assertion. Therefore, absent any evidence to the contrary, there would have been a reasonable expectation in making such a construct from the combined teachings of Dong et al and Glorioso et al comprising a deletion in the gene encoding ICP27 as well as AAV cap/rep coding sequences, and in using such a construct to produce rAAV.

In response to applicant's argument that the motivation to experiment with deletions, deletions of different genes in HSV or with different constructs was a challenge to Applicants to improve rep and cap inducible cell lines because current procedures utilizing rep and cap plasmids had a tendency to generate wild-type AAV, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). The motivation of Dong et al to make their recombinant HSV constructs comprising AAV rep and cap sequences was to provide

means of producing rAAV in which the transfection step for plasmids bearing rep and cap could be eliminated in favor of the far more efficient step of providing these essential AAV sequences by viral infection. Clearly, the use of an HSV construct comprising copies of AAV rep and cap to provide these essential AAV sequences to cells comprising a packageable rAAV construct would eliminate the need for a transfection step.

Regarding the assertion that despite knowledge of the genes involved, procedures for constructing expression vectors, and gene modification techniques, others have not disclosed the recombinant AAV vectors that provided high titre rAAV production, there is no limitation in the rejected claims that the claimed constructs yield high titre rAAV. Moreover, there is no scientific reason or evidence of record that an HSV construct made from the combined teachings of Dong et al and Glorioso et al would not itself yield high-titre rAAV stocks when used in the methods taught by Dong et al for production of rAAV.

Regarding the limitation of comprising a mutation in the IE63 gene encoding ICP27 (i.e. the ICP27 or α27 gene), there is no evidence or argument of record that would contradict the expectation that an ICP27 deletion mutant as taught by Glorioso et al would not also result in increased expression of the ICP8 protein in the same manner as the d27.1 mutation. Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior

art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claims 41-48, 50-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dong et al in view of Rice et al (J. Virol. 1990, Vol. 64, No. 4, pages 1704-1715; see the entire document). **This is a new rejection necessitated by applicants amendment of 10/3/00.**

This rejection is applied to claims 41-45 in that it is unclear whether the term "rHSV d27.1rc" is meant as only an example of an ICP27 deletion mutant of the invention or whether the claims are directed solely to the embodiments comprising the specific construct d27.1rc HSV described in the specification. This rejection applies to the broader limitation of "A herpes simplex virus ICP27 deletion mutant..".

The teachings of Dong et al are described above and applied as before, except:

Dong et al do not teach the use of the HSV d27.1 mutant as the backbone of their HSV construct featuring a mutation in at least one essential gene and also comprising AAV rep and cap sequences.

Rice et al teach the isolation and characterization of a series of HSV mutants comprising alterations in the ICP27 coding sequence. Rice et al teach a number of point mutants within the ICP27 coding sequence as well as a mutant, d27.1, having a deletion of the promoter region and most of the coding sequence (e.g. Figure 1). Rice et al teach that ICP27 is required for lytic replication, that ICP27 mutants do not replicate HSV DNA at wildtype levels, the ICP27 mutants

can be complemented by cells engineered to express ICP27 (e.g. V27 cells) and that for all but one of the point mutants of ICP27, levels of expression for ICP8 are increased. Rice et al teach that this effect on ICP8 expression has been observed in the prior art for at least one other deletion mutant of ICP27 (Abstract; page 1713, column 2; page 1713, column 1, Negative regulation of α and B gene expression by ICP27).

It would have been obvious to one of ordinary skill in the art at the time of the invention was made to construct an HSV mutant comprising a mutation in an essential gene for HSV replication as well as AAV rep and cap sequences as taught by Dong et al by utilizing one of the ICP27 mutants taught by Rice et al because Dong et al teach it is within the skill of the art to construct and use such an HSV helper virus comprising a deletion is an essential gene for HSV and because Rice et al teach it is within the skill of the art to construct deletion mutants of HSV comprising mutations in the ICP27 gene such that the HSV ICP27 mutants can be complemented/propagated in appropriate cell lines and which are replication deficient in non-complementing cells. One would have been motivated to do so in order to receive the expected benefit of generating an HSV helper construct comprising a mutation in an essential HSV gene as well as comprising the AAV rep and cap sequences, as taught as a preferred embodiment by Dong et al and featuring a well-characterized mutation in the essential ICP27 gene, as characterized by Rice et al. Such an ICP27 construct would reasonably be expected to direct the non-complementing host cell's machinery primarily to production of rAAV in the methods taught by Dong et al due to the limiting effects of the ICP27 mutation on HSV replication, as taught by

Rice et al. Based upon the combined teachings above, and absent any evidence to the contrary, there would have been a reasonable expectation of success in constructing and using an HSV helper virus according to the teachings of Dong et al and featuring mutation of the ICP27 gene sequence as taught by Rice et al.

Claims 46 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dong et al in view of Efstathiou et al (U.S. Patent No. 5,928,913; see the entire document). **This is a new rejection necessitated by applicants' amendment of 10/3/00.**

The teachings of Dong et al are described above and applied as before, except:

Dong et al don't specifically teach an HSV construct comprising a mutation such that the mutant does not express glycoprotein H.

Efstathiou et al teach a number of different HSV amplicons which require the assistance of a helper virus for their propagation. Such a helper virus is of restricted replication competence in a normal host cell (Abstract). The patent teaches that such helper viruses can comprise mutations in genes required for the formation of infectious virions (e.g. gB, gD, gH, gL, ICP4, ICP8 and/or ICP27) and that replication of such mutants requires complementation with the essential gene product in recombinant host cells expressing the essential gene product (column 5). Efstathiou et al teach a specific embodiment comprising a gH deletion mutant virus (columns 20-21).

It would have been obvious to one of ordinary skill in the art at the time of the invention to construct an HSV mutant comprising a mutation of an essential gene as well as AAV rep and cap sequences, as taught by Dong et al, by utilizing the gH deletion mutants taught by Efstathiou et al because Dong et al teach it is within the skill of the art to construct and utilize an HSV mutant comprising a mutation in an essential gene as well as comprising AAV rep and cap sequences to provide helper functions for rAAV, and because Efstathiou et al teach it is within the skill of the art to construct HSV mutants comprising a deletion of the essential gene encoding glycoprotein H. One would have been motivated to do so in order to receive the expected benefit of utilizing an HSV construct comprising a mutation in an essential gene such that the construct does not result in the production of infectious HSV particles, as taught by Efstathiou et al, while providing helper functions for the production of rAAV particles, as taught by Dong et al.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald Leffers, Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on Monday through Friday, from about 9:00 AM to about 5:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GLJ

G. Leffers, Jr.
Patent Examiner
Art Unit 1636

February 26, 2001

DAVID GUZO
PRIMARY EXAMINER

SUGGESTION FOR DEPOSIT OF BIOLOGICAL MATERIAL ATTACHMENT

A declaration by applicant or assignee, or a statement by applicant's agent identifying a deposit of biological material and averring the following may be sufficient to overcome an objection or rejection based on a lack of availability of biological material. Such a declaration:

1. Identifies declarant.

2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. The depository is to be identified by name and address. (See 37 C.F.R. § 1.803).

3. States that the deposited material has been accorded a specific (recited) accession number.

4. States that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of the patent. (See 37 C.F.R. § 1.808(a)(2)).

5. States that the material has been deposited under conditions that assure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. § 1.14 and 35 U.S.C. § 122. (See 37 C.F.R. § 1.808(a)(1)).

6. States that the deposited material will be maintained with all the care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case, for a period of at least thirty (30) years after the date of deposit or for the enforceable life of the patent, whichever period is longer. See 37 C.F.R. § 1.806).

7. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Alternatively, it may be averred that deposited material has been accepted for deposit under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (e.g., see 961 OG 21, 1977) and that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of a patent.

Additionally, the deposit must be referred to in the body of the specification and be identified by deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.